Remarks

Amendments to the Claims

Claim 1 has been amended to incorporate the limitation of claim 3 and the language at page 4, lines 3-11 and page 11, lines 1-7. Claim 3 has been amended to define the diketopiperazine coated with a polymer. Support is found at page 4, lines 1-2. Claim 4 has been amended to correct the dependency.

Rejection Under 35 U.S.C. § 112, second paragraph

Claim 18 was rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claim as amended. Claim 18 has been amended to correct an obvious typographical error. Support for this amendment can be found in original claim 18 as filed. Claim 18 as amended is definite.

Rejections Under 35 U.S.C. § 102

Claims 1-36 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 6,071,497 to Steiner, et al. ("the '497 patent") and claims 1-7, 11-27 and 34-36 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,652,885 to Steiner, et al. ("the '885 patent"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

For a rejection of claims to be proper under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic*

& Research Found v Genentech Inc, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to make and use the invention. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled". *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003).

In order to establish inherency, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or

characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, ***and that it would be so recognized by persons of ordinary skill***. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis added)

Analysis

The claims as amended define a method for enhancing transport of a compound across a membrane of lipid bilayer, comprising

forming a complex comprising the compound and an effective amount of diketopiperazine (DKP) to enhance transport

wherein transport of the compound from the proximal face of the lipid bilayer to a distal face of the lipid bilayer is increased in the presence of the DKP compared to in the absence of the DKP

and administering the complex using a schedule resulting in substantially no increase in immune response.

The prior art does not recognize that transport can be enhanced, with substantially no increase in immune response, through complexation of a defined amount of diketopiperazine with the material to be delivered, which is delivered using a defined schedule. See general discussion at pages 10-11, and examples at pages 11-19, especially example 8.

The '497 patent

The '497 patent describes a drug delivery system comprising a complex of diketopiperazine and drug to be delivered. The complex is formed by co-precipitation or absorption of the drug to the diketopiperazine. This complex is then lyophilized to form a dry powder suitable for pulmonary administration.

The '497 patent does not disclose or suggest a method for enhancing transport of a compound across a membrane or lipid bilayer comprising forming a complex containing the compound and DKP. Furthermore, nowhere in the '497 patent is there any teaching that complexation with diketopiperazine can enhance transport through a lipid bilayer. Second, there is no indication in the '497 patent that uptake will be enhanced by the diketopiperazine, only that there will be uptake - indeed, there is a suggestion that it will be adequate but less than that which occurs with injection of the same drug. There is nothing with respect to avoiding any increase in immune response, much less how to achieve this.

Since at least two of the claimed elements, enhancing uptake and avoiding an increase in immune response, in the independent claims is not present in the reference, the reference cannot anticipate.

There is certainly no recognition in the '497 patent of how much uptake will be enhanced, nor that it will not elicit an immune response, nor that a defined schedule of administration should be followed, as defined by the dependent claims in the present application (which the examiner seems to have overlooked, the rejection being made under 102(b).

Therefore, claims 1-36 are not anticipated by the '497 patent.

The '885 patent

The '885 patent describes a method for purifying peptides and proteins by incorporating them into diketopiperazines to facilitate removal of one or more impurities.

The '885 patent does not disclose or suggest a method for enhancing transport of a compound across a membrane or lipid bilayer or contacting the proximal face of a membrane or bilayer with a diketopiperazine-drug complex. The '885 patent does not disclose or suggest that the compound can be transported through a lipid bilayer faster in the presence of diketopiperazine that in the absence of diketopiperazine. There is nothing with respect to avoiding any increase in immune response, much less how to achieve this.

Therefore, claims 1-36 are not anticipated by the '885 patent.

Rejection Under 35 U.S.C. § 103

Claims 1-36 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the '497 patent, in view of the '885 patent. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). **To establish a *prima facie* case of obviousness, three basic criteria must be met.** First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In addition, references relied upon to support a rejection under 35 U.S.C. § 103 must provide an enabling disclosure, i.e., "they must place the claimed invention in the possession of the public." *Application of Payne*, 606 F.2d 303, 314, 203 U.S.P.Q. 245 (C.C.P.A. 1979); *see Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 13 U.S.P.Q.2d 1301 (Fed. Cir. 1989). A publication that is insufficient as a matter of law to constitute an enabling reference

may still be relied upon, but only for what it discloses. *See Reading & Bates Constr. Co. v. Baker Energy Resources Corp.*, 74 8 F.2d 645, 651-652, 223 U.S.P.Q. 1168 (Fed. Cir. 1984); *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991).

The courts have warned that "Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *See In re Geiger* , 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

It is clear that to establish a rejection under 35 U.S.C. § 103 the cited references must (1) recite each and every element of the claims, (2) provide one of skill in the art with the motivation to combine the cited references and (3) provide one of ordinary skill in the art with a reasonable expectation of success. The references cited by the Examiner clearly do not meet all three criteria.

(1) recite each and every element of the claims

As discussed above, the '497 patent nor the '885 patent disclose or suggest a method for enhancing transport of a compound across a membrane of lipid bilayer comprising forming a complex containing a compound and DKP, much less how to administer the complex to avoid an immune response. Therefore, since the references do not disclose or suggest every element of the claims as amended, the claims are not obvious over the '497 and '885 patents.

(2) provide one of skill in the art with the motivation to combine the cited references and (3) with a reasonable expectation of success

There is nothing in the '497 or '885 patents to provide one of ordinary skill in the art with the motivation to combine the references. There is nothing at all about avoiding an immune response. Even if one combined the references one would still not have any knowledge of how to administer the complex to avoid an increase in immune response. The examples demonstrate that the amount of DKP, the conditions of complex formation, and the time and amount of administration, determine the immune response. Therefore, one of ordinary skill in the art is not provided with a reasonable expectation of success that a complex of compound and DKP can result in enhanced transport of the compound across a membrane or lipid bilayer without an

increase in immune response. The '497 patent does not disclose or suggest using DKP molecules to enhance uptake of a compound. The '885 patent does not disclose or suggest that the compound can be transported through a lipid bilayer faster in the presence of diketopiperazine that in the absence of diketopiperazine. Therefore, claims 1-36 are not obvious over the '497 and '885 patents.

Allowance of claims 1-36 is respectfully solicited.

Respectfully submitted,

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